

REMARKS:

In the Office Action dated March 14, 2007, claims 34, 42, 43, 51, 59, 60, 62 and 63, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-64 have been canceled and new claims 65 -71 have been added to the application.

Claims 42 and 43 were objected to as being of improper dependent form. Claims 42 and 43 have been canceled and new claims added to the application which more clearly indicate that fusion polypeptides comprising the recited polypeptide are encompassed by the present claims. Regarding the term "recombinant polypeptide", applicants respectfully point out that this term further limits the term "polypeptide" as a polypeptide can be natural or recombinant. In view of the cancellation of claims 42 and 43 and the addition of new claims to the application, applicants request that this rejection be withdrawn.

Claims 34, 42, 43, 51, 59, 60, 62 and 63 were rejected under 35 USC §112, first paragraph. Applicants respectfully point out that the present inventors started with a large collection of mutagenized *Drosophila* strains having an expression system (EP-element) randomly integrated in different genomic loci. Example 1 in the present application describes a measurement of triglyceride content in mutagenized *Drosophila* strains. According to this technique, a fly strain HD-EP (3)31805 was identified which had a significantly higher triglyceride content than the controls (Figure 1). This elevated triglyceride content is caused by a modulation of gene activity in the locus where the EP-vector is integrated.

Example 2 describes the identification of *Drosophila* genes associated with the observed increased triglyceride content in fly strain HD-EP31805. It was found that the

EP-vector 31805 is homozygously integrated in the locus of a *Drosophila* gene identified as CG7956. Example 3 describes the identification of the Sac domain-containing inositol phosphatase 2 (SAC2) gene as a human CG7956 homolog. Example 6 describes an expression analysis of the SAC2 gene in mouse tissues. The results are shown in Figures 4A and 4B. The data in Figure 4B shows that SAC2 is upregulated in brown fat tissue (BAT) and the pancreas of fasted animals and ob/ob mice. In addition, a high expression level of SAC2 in the hypothalamus and white adipose tissue (WAT) was found. This is a clear indication that the SAC2 gene plays a central role in the energy homeostasis of mammalian organisms. Furthermore, this is evidence that metabolic diseases and dysfunction are associated with altered SAC2 expression in relevant tissues. Thus, applicants respectfully contend that the claimed therapeutic effect is demonstrated in the Examples of the present application.

As discussed above, evidence can be found in the data obtained from *Drosophila*. The *Drosophila* CG7956 gene was identified by its biological function, namely its relation to triglyceride metabolism. *Drosophila* is an established model for physiological studies in vertebrates as evidenced by Hafen and Suh et al. (copies submitted herewith). Hafen is a review article which refers to the importance of *Drosophila* and *Caenorhabditis elegans* as model organisms for the understanding of pathology-relevant signal transduction pathways in higher organisms. Particular reference is made to the evolutionary conservation of nutrient-dependent growth regulation. Suh et al. indicates that signal transduction pathways of the adipocyte metabolism are highly conserved in *Drosophila* and vertebrates. Thus, biological data in *Drosophila* allow predictions of the functions of highly conserved genes in higher

organisms, e.g. mammals. Applicants therefore contend that due to the high conservation of metabolic processes in *Drosophila* and mammals, biologic data obtained in *Drosophila* correlates with expected results in vertebrate organisms including humans.

The present application also includes mammalian expression data. This data shows a modified SAC2 expression associated with metabolic disturbances such as fasting or obesity. Based on the above discussed *Drosophila* and mammalian expression data, one skilled in the art would determine that a SAC2 gene is suitable for the treatment of metabolic disorders.

In addition, new biological data ("CG7956 Homolog in Vitro Validation") is submitted herewith. A declaration discussing this data will be submitted shortly. This data was obtained through experiments involving a study of the effects of RNAi mediated loss of function in 3T3-L1 adipocytes. From these experiments the following biological activities of SAC2 in mammalian cells was determined:

- a knockout of SAC2 by an RNAi molecule leads to a decreased expression of adipocyte markers such as PPARgamma (Figure 1) and aP2 (Figure 2) throughout adipogenesis,
- a SAC2 knockout results in a decreased triglyceride content (Figure 3) through adipogenesis,
- a SAC2 knockout reduces the free fatty acid uptake in adipocytes (Figure 4) and
- a knockout of SAC2 leads to an increase of insulin-stimulated glucose uptake (Figure 5).

This additional data confirms the effect of the claimed method with regard to metabolic diseases or dysfunctions, particularly relating to the triglyceride and/or glucose metabolism. In view of the above discussed data, applicants request that this rejection be withdrawn.

Regarding how a human homolog of the gene product of *Drosophila* Accession No. CG7956 protein which has only 52% homology to human Sac domain-containing inositol phosphatase protein would have the desired activity, applicants respectfully point out that more than 650 million years of evolution lie between homologous genes of *Drosophila* and humans. Thus, homology values of about 50% are already relevant with respect to function. Additionally, further aspects must be taken into account like length of the sequence and if it relates to the whole protein, only to a domain or to a protein class.

Examples exist where the three dimensional structures of proteins and their function therewith are substantially unchanged even if their sequences have an identity of less than about 20%. A sequence identity of less than 20%, however, is below the detection limit of sequence homology. Usually, an identity of less than 30% is regarded as an indication of a change of function. However, the value of homology alone is not relevant in order to identify a *Drosophila* ortholog. Much more important are BLAST searches, multiple alignments of protein families and phylogenetic trees. With respect to the sequence identities of orthologs, the following has been published:

Drosophila vs *Anopheles*, 250 million years: "Almost half of the genes in both genomes are interpreted as orthologs and show an average sequence identity of about 56%, which is slightly lower than that observed between the orthologs of the puffer-fish

and human (diverged about 450 million years ago)" ("Comparative Genome and Proteome Analysis of *Anopheles gambiae* and *Drosophila melanogaster*", Science 4 October 2002: Vol. 298, No. 5591, pp. 149-159).

Chicken vs. Human, 310 million years: "About 60% of chicken protein-coding genes have a single human orthologue; for the remainder, orthology relationships are more complex or are not detectable. Chicken and human 1:1 orthologue pairs exhibit lower sequence conservation (median amino acid identity of 75.3%) than rodent and human 1:1 orthologue pairs (88%), as expected. Orthologous sequences involved in cytoplasmic and nuclear functions are more conserved than those implicated in reproduction, host defense and adaptation to the environment ("Sequence and comparative analysis of the chicken genome provide unique perspectives on vertebrate evolution", International Chicken Genome Sequencing Consortium, http://www.bx-psu.edu/miller_lab/dist/chicken.pdf).

Claims 34, 42 and 43 were rejected under 35 USC §112, first paragraph, regarding the treatment, alleviation and/or prevention of metabolic diseases. Claims 34, 42 and 43 have been canceled and new claims added to the application. The new claims are directed to the treatment of metabolic diseases or to a method for regulating triglyceride metabolism and/or adipogenesis. As discussed above, in view of the *Drosophila* and mammalian expression data in the present application, one skilled in the art would reasonably conclude that a SAC2 gene is suitable for the treatment of metabolic disorders. In view of the cancellation of claims 34, 42 and 43 and the above comments, applicants request that this rejection be withdrawn.

Claims 34, 43 and 60 were rejected under 35 USC §112, second paragraph, as

indefinite. Claims 34, 43 and 60 have been canceled and new claims added to the application. The new claims do not include most of the language found indefinite. However, applicants point out that the language "recombinant polypeptide" in new claim 67, refers to the recombinant polypeptide of claim 66 and thus has antecedent basis. In view of the cancellation of claims 34, 43 and 60, applicants request that this rejection be withdrawn.

Claims 34, 42, 51, 59, 62 and 63 were rejected under 35 USC §102(b) as unpatentable over Nagase. Nagase does not suggest or disclose the use of a CG7956 nucleic acid molecule or a peptide encoded thereby for the treatment of metabolic diseases or dysfunctions or for regulating triglyceride metabolism and/or adipogenesis. Claims 34, 42, 51, 59, 62 and 63 have been canceled and new claims added to the application directed to methods for the treatment of metabolic diseases or dysfunctions or for regulating triglyceride metabolism and/or adipogenesis. In view of the cancellation of claims 34, 42, 51, 59, 62 and 63, applicant requests that this rejection be withdrawn.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By



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